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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/620,691	07/20/2000	David A. Tirrell	30431.5US01	3160

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EXAMINER	
GUPTA, ANISH	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/620,691	TIRRELL ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *08 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. The amendment filed 8-8-03 has been acknowledged. Claims 1, 3, 4 were amended. Claims 15-24 were added and claim 2 was canceled. Claims 1, 3-4, and 15-24 are pending in this application.

2. All rejections cited in the previous office action and not cited herein are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4 remain rejected and 15-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous office action and the reasons set forth below.

For the rejection, Applicants argue that the specification provides representative polypeptides that contain "leucine zipper domains, membrane proteins" and "cytokines such as interleukins, Tumor Necrosis Factor, Granulocyte colony Stimulating Factor, Erythropoitin, protease such as Subtilisin, Termolysin, industrial enzymes such as dehydrogenases, estrases." Further, Applicants make reference to the incorporation of the non-natural amino acid in the "region(s) containing hydrophobic amino acid that generally drive protein folding." Applicants state

that using known chemical methods such as solid-phase synthesis or native chemical ligation will yield the desired product. It is emphasized that the specification "uses two α-helical polypeptides, GCN4-p1 and A1, as representative of leucine zipper family and coiled coil proteins. Applicants respectfully points out that the examples of GCN4-p1 and A1 not only provide representative polypeptides but also provides representative examples with respect to the level or amount of incorporating non-natural amino acids in the polypeptides."

Applicant's arguments filed 8-8-03 have been fully considered but they are not persuasive. Although the specification has provided examples of sequences that may be used, the specification does not provide examples interleukins, Tumor Necrosis Factor, Granulocyte colony Stimulating Factor, Erythropoitin that have incorporated in them a non-natural amino acid. Applicants state that the incorporation takes place in the hydrophobic region of the peptide. However, it is unclear what comprises this hyrdrophobic region. For example, the sequence for human TNF is:

> MSTESMIRDV ELAEEALPKK TGGPQGSRRC LFLSLFSFLI VAGATTLFCL
> LHFGVIGPQR EEFPRDLSLI SPLAQAVRSS SRTPSDKPVA HVVANPQAEG
> QLQWLNRRAN ALLANGVELR DNQLVVPSEG LYLIYSQVLF
> KGQGCPSTHVLLTHTISRIA VSYQTKVNLL SAIKSPCQRE TPEGAEAKPW
> YEPIYLGGVFQLEKGDRLSA EINRPDYLDF AESGQVYFGI IAL.

It is unclear which portion of sequence would comprise the hydrophobic region. Note that the sequence is replete with Leucine, phenylalanine, isoleucine, valine and methionine. It is unclear if two hydrophobic amino acids next to one another render a hydrophobic region or more hydrophobic amino acids are required. This is similarly true for GCSF and erythropoitin. The specification does not provide any examples of modified peptides that would indicate to one of

ordinary skill in the art that Applicants were in possession of any polypeptide in which a leucine, isoleucine, valine, phenylalanine were substituted with a non-naturally occurring amino acid. Applicants argue that the specification provides two examples that illustrate the claimed invention. These two peptides however do not provide sufficient support for a broad generic. As stated in the previous office action, it has been indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of **two chemical** compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618. Further, the presence of isoleucine, leucine or valine would not be sufficient to form a common core since one could not readily envisage a representative number of examples with this common core. Further, the polypeptide and proteins of the claims are not limited to any specific class of compounds for which one could readily obtain physical and/or chemical properties or functional characteristics thereby obtaining some insight as to the structure of the desired proteins or polypeptide. It is noted that the specification states that the proteins and polypeptide envisaged contain a hydrophobic core. However, the specification does not describe what amino acids and how many amino acids constitute this hydrophobic core.

Rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

a person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 3-4 remain rejected and new claim 15-16, 23 under 35 U.S.C. 102(b) as being anticipated by Rennert et al.

The claims are drawn to a polypeptide wherein a leucine, isoleucine or valine are substituted with a non-natural amino acids.

Applicants argue Rennet does not "specifically teach or disclose a 'polypeptide comprising at least on non-natural amino acid causes an increase in the thermal stability of the polypeptide as compared with a corresponding wild type polypeptide not having the non-natural amino acid." Applicants state that the reference does not specifically describe any particular protein that incorporates non-natural amino acids.

Applicant's arguments filed 8-8-03 have been fully considered but they are not persuasive.

Rennet states 'in the modified chemostat E. coli can be adapted to grow at normal rates on a medium containing only trifluoroleucine, and under these conditions Leucine in the proteins is entirely replaced by trifluoroleucine" (see abstract). Thus the reference discloses a protein that have incorporated in them trifluoroleucine. Applicants stress that the reference is silent about the thermal stability. However, such a recitation is merely a characteristic or the functional limitation for the incorporation of the non-naturally occurring amino acid. The MPEP states, where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. In re Best, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the

claimed product. In re Best, *supra*. Here, the reference teaches all of the structural limitations of the claims, i.e. protein wherein a non-natural amino acid (trifluroleucine) is substituted in the hydrophobic region (Leucine), and thus the protein would inherently have the claimed characteristics. Applicants have not met their burden to show the prior art products do not necessarily possess the characteristics of the claimed product.

Applicants have stated that the reference does not disclose a specific protein. However, this rather similar to Applicants claimed invention which similarly does not claim any specific protein or sequence. Thus, so long as a single amino acid has be substituted in the hydrophobic region with a non-naturally occurring amino acid, the reference meet the limitations of the claim. Here, the reference discloses the replacement of leucine with 5,5,5 trifluoroleucine in an E.coli B protein. (See page 471). The Leucine is a hydrophobic amino acid and trifluoroleucine is a preferred embodiment of claim 4.

Rejection is maintained.

2. Claims 1 and 3-4 remain rejected and new claims 15-16 and 23 are under 35 U.S.C. 102(b) as being anticipated by Russel et al.

The claims are drawn to a polypeptide wherein a leucine, isoleucine or valine are substituted with a non-natural amino acids.

Applicants argue that the reference does not "disclose or describe any proteins that have an increased thermal stability when compared to their wild-type counterpart. Further Russell et al., does not teach or describe any proteins, including leucine zippers or coiled-coil proteins, let alone such proteins that have incorporated non-natural amino acids...To Applciants' knowledge, gramicidin A is neither a leucine zipper nor a coiled-coil protein."

Applicant's arguments filed 8-8-03 have been fully considered but they are not persuasive.

Firstly, the claims have not been limited to protein having a leucine zipper or coiled-coil locations and specifically substituting into these regions a non-naturally occurring amino acid. Thus, arguments with this regard are totally unpersuasive. The reference discloses that the N-terminal valine was replaced in the gramicidin A analog with trifluorovaline or hexafluorovaline. The N-terminal amino acid sequence of gramicidin A is Val-Gly-Ala-D-Leu-Ala-D-Val. . .. It is conventionally known in the art that glycine is neutral and ala is weakly hydrophobic. Thus the nature of the N-terminus of the Gramicidin would be hydrophobic. Accordingly, the reference by virtue of teaching the replacement of the N-terminal valine with trifluorovaline or hexafluorovaline in an gramicidin a meets all of the structural limitations of the claim. Applicants stress that the reference is silent about the thermal stability. However, such a recitation is merely a characteristic or the functional limitation for the incorporation of the non-naturally occurring amino acid. The MPEP states, where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. In re Best, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, *supra*. Here, the reference teaches all of the structural limitations of the claims, i.e. replacement of the N-terminal valine with trifluorovaline or hexafluorovaline in the hydrophobic region of gramicidin a, and thus the modified peptide would inherently have the claimed characteristics. Applicants have not met

their burden to show the prior art products do not necessarily possess the characteristics of the claimed product.

Rejection is maintained.

3. Claims 1 and 3-4 remain rejected and new claims 15-16 and 23 are under 35 U.S.C. 102(b) as being anticipated by Arai et al.

The claims are drawn to a polypeptide wherein a leucine, isoleucine or valine are substituted with a non-natural amino acids.

For this reference Applicants make similar arguments made for Russell, i.e. that the reference does not disclose or describe any proteins that have an increased thermal stability when compared to their wild-type counterpart.

Applicant's arguments filed 8-8-03 have been fully considered but they are not persuasive.

The reference discloses the replacement of to valine residues in natural gramicind S with hexafluorovaline. (See abstract). Note that the location of valine would qualify as a "hydrophobic region" since the replaced valine is next to Proline, D-phenylalanine, and Leucine, which are hydrophobic amino acids. Thus, the reference discloses the replacement of a hydrophobic amino acid (valine) in a hydrophobic region with a hexaflurovaline residue. Applicants stress that the reference is silent about the thermal stability. However, such a recitation is merely a characteristic or the functional limitation for the incorporation of the non-naturally occurring amino acid. The MPEP states, where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. In re Best, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the

burden of showing that they are not." In re Spada, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, *supra*. Here, the reference teaches all of the structural limitations of the claims, i.e. replacement of the N-terminal valine with hexafluorovaline in the hydrophobic region of gramicidin S, and thus the modified peptide would inherently have the claimed characteristics. Applicants have not met their burden to show the prior art products do not necessarily possess the characteristics of the claimed product.

4. Claims 1 and 3-4 remain rejected and 16 under 35 U.S.C. 102(b) as being anticipated by Mendel et al.

The claims are drawn to a polypeptide wherein a leucine, isoleucine or valine are substituted with a non-natural amino acids.

For this reference Applicants make similar arguments made for Russell, i.e. that the reference does not disclose or describe any proteins that have an increased thermal stability when compared to their wild-type counterpart.

Applicant's arguments filed 8-8-03 have been fully considered but they are not persuasive.

The reference discloses the replacement of a leucine with a S,S-2-amino-4-methylhexanoic acid in the 133 position in the T4 Lysozyme (See page 1799-1800). The S,S-2-amino-4-methyhexanoic acid is a hydrophobic amino acid. In T4 Lysozyme the sequence in position 128-134 have the sequence AAVNLA. This area of the sequence can be construed as a hydrophobic region because of the number of hydrophobic amino acids present. Thus, the reference discloses the replacement of a hydrophobic amino acid (valine) in a hydrophobic region

with a S,S-2-amino-4-methyhexanoic acid residue. Applicants stress that the reference is silent about the thermal stability. However, such a recitation is merely a characteristic or the functional limitation for the incorporation of the non-naturally occurring amino acid. The MPEP states, where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. In re Best, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, *supra.* Here, the reference teaches all of the structural limitations of the claims, i.e. replacement of the valine with S,S-2-amino-4-methyhexanoic acid in the hydrophobic region of T4 Lysozyme, and thus the modified peptide would inherently have the claimed characteristics. Applicants have not met their burden to show the prior art products do not necessarily possess the characteristics of the claimed product.

New Grounds for Rejections

5. Claims 1 and 3-4, and 15-19 are under 35 U.S.C. 102(b) as being anticipated by Miyazawa et al. (US 4879223).

The claims are drawn to a polypeptide wherein a leucine, isoleucine or valine are substituted with a non-natural amino acids.

The reference disclose modified Epidermal growth factor wherein the 21st amino acid Tyrosine is replaced with norleucine (see col. 8, lines 35-50). Note that in the native sequence of

epidermal growth factor has a methionine residue in position 21 and a isoleucine in position 23 (see attached sequence of EGF). Further note that the amino acid residues 21-23 are Met-Tyr-Ile in the native EGF. The presence of these three hydrophobic amino acid renders it a hydrophobic region. As for the thermal stability, the MPEP states, where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. In re Best, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, *supra.* Here, the reference discloses a peptide which incorporates a non-natural amino acid in the EGF molecule in the hydrophobic region.

6. Claims 1 and 3-4, 15-19 and 22 are under 35 U.S.C. 102(b) as being anticipated by Koide et al.

The claims are drawn to a polypeptide wherein a leucine, isoleucine or valine are substituted with a non-natural amino acids.

The reference teaches incorporation of fluorophenylalaine residue in hEGF in position Tyr22 and Tyr 29 (see abstract). The reference disclose the replacement of the Tyr residues with phe and then the subsequent modification of the phe residue (see abstract). As noted above, native sequence of epidermal growth factor has a methionine residue in position 21 and a isoleucine in position 23 (see attached sequence of EGF). Further note that the amino acid residues 21-23 are Met-Tyr-Ile in the native EGF. The presence of these three hydrophobic amino acid renders it a

hydrophobic region. As for the thermal stability, the MPEP states, where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. In re Best, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, *supra.* Here, the reference discloses a peptide which incorporates a non-natural amino acid in the EGF molecule in the hydrophobic region.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback , can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

10/20/05
Anish Gupta
Patent Examiner

Brenda Brumback
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